Amendments to the Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (currently amended) An isolated polypeptide, wherein said isolated polypeptide is a [[A]] single chain polypeptide comprising first and second domains, wherein said single chain polypeptide lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated H_C thereby rendering the polypeptide incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds; and wherein:- said first domain is a clostridial neurotoxin light chain or a fragment or a variant thereof, wherein said first domain is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis; and said second domain is a clostridial neurotoxin heavy chain H_N portion or a fragment or a variant thereof, wherein said second domain is capable of (i) translocating the polypeptide into a cell or (ii) increasing the solubility of the polypeptide compared to the solubility of the first domain on its own or (iii) both translocating the polypeptide into a cell and increasing the solubility of the polypeptide compared to the solubility of the first domain on its own; wherein said single chain polypeptide comprises a sequence selected from the group consisting of:-

(I) SEQ ID NO: 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 139, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, and 175; or

(II) a fragment or variant of (I) having a first domain that is capable of cleaving one or more vesicle or plasma membrane associated proteins essential to exocytosis, wherein said variant lacks a functional C-terminal part of a clostridial neurotoxin heavy chain designated Hc, thereby rendering the variant incapable of binding to cell surface receptors that are the natural cell surface receptors to which native clostridial neurotoxin binds.

2. (original) A polypeptide according to Claim 1 wherein said clostridial toxin heavy chain is a botulinum neurotoxin heavy chain.

3. (original) A polypeptide according to Claim 1 wherein said clostridial toxin heavy chain is a tetanus neurotoxin heavy chain.

4. (previously presented)A polypeptide according to Claim 1, wherein the first domain exhibits endopeptidase activity specific for a substrate selected from one or more of SNAP-25, synaptobrevin/VAMP and syntaxin.

5. (previously presented)A polypeptide according to Claim 1, wherein said second domain is a clostridial toxin heavy chain H_N portion.

6. (original) A polypeptide according to Claim 1, wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type A chain.

7. (original) A polypeptide according to Claim 1, wherein the second domain comprises the 423 N-terminal amino acids of botulinum toxin type A heavy chain.

8. (original) A polypeptide according to Claim 1, wherein said clostridial neurotoxin heavy chain is a botulinum neurotoxin type B chain.

9. (original) A polypeptide according to Claim 1, wherein the second domain comprises the 107 N-terminal amino acids of a botulinum toxin type B heavy chain.

10. (original) A polypeptide according to Claim 1, wherein the second domain comprises the 417 N-terminal amino acids of botulinum toxin type B heavy chain.

11. (original) A polypeptide according to Claim 1 wherein the second domain comprises the 422 N-terminal amino acids of tetanus heavy chain.

12. (original) A polypeptide according to Claim 1 wherein the second domain comprises the 100 N-terminal amino acids of a clostridial neurotoxin heavy chain.

13. (original) A polypeptide according to Claim 1 comprising a site for cleavage by a proteolytic enzyme.

14. (original) A polypeptide according to Claim 13, wherein the cleavage site is not present in a native clostridial neurotoxin.

15. (previously presented)A polypeptide according to Claim 13, wherein the cleavage site allows proteolytic cleavage of the first and second domains.

16. (previously presented)A polypeptide according to Claim 13, wherein the cleavage site allows proteolytic cleavage of the first and second domains, and when so cleaved said first domain exhibits greater enzyme activity in cleaving said one or more vesicle or plasma membrane associated protein than does the-polypeptide prior to said proteolytic cleavage.

17. (previously presented)A polypeptide according to Claim 13 obtainable by providing a first nucleic acid sequence encoding said cleavage site within a second nucleic acid sequence encoding said single chain polypeptide.

18. (previously presented)A polypeptide according to Claim 1, wherein said single chain polypeptide lacks a C-terminal part of a clostridial neurotoxin heavy chain designated H_C.

19. (previously presented)A polypeptide according to Claim 1, further comprising a third domain that binds the polypeptide to a cell, by binding of the third domain directly to a cell or by binding of the third domain to a ligand or to ligands that bind to a cell.

20. (original) A polypeptide according to Claim 19, wherein said third domain is for binding the polypeptide to an immunoglobulin.

21. (original) A polypeptide according to Claim 20, wherein said third domain is a tandem repeat synthetic IgG binding domain derived from domain b of Staphylococcal protein A.

22. (original) A polypeptide according to Claim 19, wherein said third domain comprises an amino acid sequence that binds to a cell surface receptor.

23. (original) A polypeptide according to Claim 22, wherein said third domain is insulin-like growth factor-1 (IGF-1).

24. (previously presented)A polypeptide according to Claim 1 including a spacer molecule between the first and second domains.

25. (previously presented)A polypeptide according to Claim 19 including a spacer molecule between the second and third domains.

26. (previously presented)A polypeptide according to Claim 1, further comprising a purification tag that binds to an affinity matrix thereby facilitating purification of the polypeptide using said matrix.

27. (original) A polypeptide according to Claim 26 including a spacer molecule between the purification tag and the polypeptide.

28. (previously presented)A polypeptide according to Claim 26, wherein said purification tag binds to an affinity matrix of glutathione sepharose.

29. (previously presented)A polypeptide according to Claim 26, wherein a first protease cleavage site is incorporated between said single chain polypeptide and the purification tag, said protease cleavage site enabling proteolytic separation of said polypeptide from said purification tag.

30. (previously presented)A polypeptide according to Claim 26, wherein a second proteolytic cleavage site is incorporated between the first and second domains of said single chain polypeptide, said protease cleavage site enabling proteolytic cleavage of the first and second domains.

31-41. (cancelled)